FORM PTO-1390	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		4121-107
		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/230929
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE97/01629	30 July 1997	2 August 1996

TITLE OF INVENTION

" VECTOR FOR ACTIVATING THE IMMUNE SYSTEM AGAINST CELLS ASSOCIATED TO PAPILLOMA VIRUSES OR SEQUENCES THEREOF"

APPLICANT(S) FOR DO/EO/U.S. Patent and Trademark Office

KLEINSCHMIDT, Jürgen, JOCHMUS, Ingrid, GISSMANN, Lutz, MÜLLER, Martin

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).*
10. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A small entity statement.
16. ☐ Other items or information:

NOTE: This application is being filed without an Oath or Declaration under the provisions of 37 CFR § 1.53 in order that applicants may secure a filing date of February 1, 1999. Upon receipt of a "Notice to File Missing Parts - Filing Date Granted," a Declaration and Power of Attorney, and an Assignment in favor of applicants' assignee, Deutsches Krebsforschungszentrum Stiftung Des Öffentlichen Rechts, will be filed in the Patent and Trademark Office. The undersigned agent affirmatively states that he has been duly authorized and appointed to file this application on behalf of the applicants and applicants' assignee, and that the Declaration and Power of Attorney to be filed hereafter will confirm the undersigned agent's authorization and appointment. Deutsches Krebsforschungszentgrum Stiftung Des Öffentlichen Rechts is a small business entity within the meaning of 37 CFR § 1.9, and an appertaining small entity statement will also be submitted for such assignee in response to a Notice to File Missing Parts.

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $0.00		
No International preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $0.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,070.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$0.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 970.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	13 -20 =	0	X **$18.00**	$ 0.00	
Independent Claims	1 -3 =	1	X **$78.00**	$ 0.00	
Multiple dependent claim(s) (if applicable)			+ **$260.00**	$ 260.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1230.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 615.00	
SUBTOTAL =				$ 615.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 615.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEE ENCLOSED =				$ 615.00	
				Amount to be: refunded	$
				Charged	$

a. ☒ A check in the amount of $ 615.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-3284. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not yet been met, a petition to revive (37 CFR 1.127(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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STEVEN J. HULTQUIST
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• K 2639 •

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(e)4 & 1.27(d)) - - FOREIGN NON PROFIT ORGANIZATION

Docket No. 4121-107

Applicants: KLEINSCHMIDT, Jürgen, JOCHMUS, Ingrid, GISSMANN, Lutz, MÜLLER, Martin

Title: **"VECTOR FOR ACTIVATING THE IMMUNE SYSTEM AGAINST CELLS ASSOCIATED TO PAPILLOMA VIRUSES OR SEQUENCES THEREOF"**

Filing Date: **February 1, 1999 (EXPRESS MAIL FILING UNDER 37 CFR 1.10)**

I hereby declare that I am:

☐ the owner of the foreign non-profit organization identified below:

☒ an official of the foreign non-profit organization empowered to act on behalf of the concern identified below:

NAME OF NON-PROFIT ORGANIZATION: **Deutsches Krebsforschungszentrum Stiftung Des Offentlichen Rechts**

ADDRESS OF NON-PROFIT ORGANIZATION: **Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany**

I hereby declare that the above identified foreign non-profit organization qualifies as a non-profit organization as defined in 37 CFR 1.9(e), for purposes of paying reduced fees to the United States Patent and Trademark Office.

I hereby aver that exclusive rights under contract or law have been conveyed to and remain with the foreign non-profit organization identified above with regard to the invention described in:

☒ The United States patent application filed on February 1, 1999 with title as listed above, based on international patent application number PCT/DE97/01629 filed 30 July 1997, and claiming priority of German patent application no. 196 31 357.0 filed 2 August 1996 (35 U.S.C. §371).

☐ Application Serial No. _____ filed _____.

☐ U.S. Patent No. _____ Issued _____.

If the rights held by the above-identified non-profit organization are not exclusive, each individual, concern, or organization having rights in the invention must file separate verified statements averring to their status as small entities, and that no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a non-profit organization under 37 CFR 1.9(e).

Each person, concern or organization having any rights in the invention is listed below:

☒ No such person, concern, or organization exists.

☐ Each such person, concern or organization is listed below:

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities (37 CFR 1.27).

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at any time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate (37 CFR 1.28(b).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Prof.Dr.med.Dr.h.c.mult.N. zur Hausen Dr.rer.pol. J. Puchta

TITLE OF PERSON IF OTHER THAN OWNER Chairman a/ Scient Member of the Board Adm.Member of the Board

ADDRESS OF PERSON SIGNING Eichenstraße 1, 69483 Waldmichelbach; Eichenweg 12a, 69198 Schriesheim

SIGNATURE _____ DATE February 23, 1999

4121-107
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	KLEINSCHMIDT, Jürgen, JOCHMUS, Ingrid, GISSMANN, Lutz, MÜLLER, Martin
Application No.:	New U.S. National Stage Application of PCT International Application No. PCT/DE97/01629
International Filing Date:	30 July 1997
Priority Date Claimed:	2 August 1996 (German Appl. No. 196 31 357.0)
U.S. National Phase Filing Date:	1 February 1999
Title:	**" VECTOR FOR ACTIVATING THE IMMUNE SYSTEM AGAINST CELLS ASSOCIATED TO PAPILLOMA VIRUSES OR SEQUENCES THEREOF"**

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that the attached documents are being mailed by such person to the Assistant Commissioner for Patents on the date specified, in an envelope addressed to the Assistant Commissioner for Patents, Box PATENT APPLICATION, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR ~~1.10.~~

Jacqueline Bagwell
Signature

Jacqueline BAGWELL
Name of Person Mailing This Document

February 1, 1999
Date of Mailing

EL 254577619 US
Express Mail Label Number

PRELIMINARY AMENDMENT IN UNITED STATES PATENT APPLICATION (NATIONAL PHASE PROCEEDINGS UNDER 35 U.S.C. § 371) BASED ON INTERNATIONAL APPLICATION NO. PCT/DE97/01629 AND CLAIMING PRIORITY OF GERMAN PATENT APPLICATION NO. 196 31 357.0

Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, DC 20231

Sir:

Preliminary to examination of this application, please cancel claims 1-15 of the original text of International Patent Application No. PCT/DE97/01629, and substitute therefor the Amended Claims

1-13 appended to the "Translation of the relevant parts of the PCT Preliminary International examination report, dated November 3, 1998."

The examination and prosecution of this application therefor are requested to be established on the basis of such Amended Claims 1-13.

Steven J. Hultquist
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Attorney for Applicants

**INTELLECTUAL PROPERTY/
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Attorney File: 4121-107

Vector for Activating the Immune System Against Cells Associated to Papilloma Viruses or Sequences Thereof

The present invention relates to a vector suited for activating the immune system against cells associated to papilloma viruses and sequences thereof, respectively, a vaccination agent which contains such a vector and the use of both.

Papilloma viruses infect the epithelium of man and animal. Human papilloma viruses (HPVs) are found in benignant, e.g. warts, condylomas in the genital region, and malignant, e.g. carcinomas of skin and uterus, epithelial neoplasms. HPVs are also considered for the development of malignant tumors of the respiratory system. In addition, HPVs are considered to be at least jointly responsible for the development of squamous carcinomas of the lungs.

Papilloma viruses have an icosahedral capsid without coat which has a circular double-stranded DNA molecule of about 7900 bp. The capsid comprises a major capsid protein (L1) and a minor capsid protein (L2). The former is coded by the open reading frame L1 (L1-ORF) and the latter is coded by L2-ORF. L1 or L1 and L2 result *in vitro* in the formation of virus-like particles (VLPs).- The transformation ability of papilloma viruses is ascribed to the proteins E6 and E7. They are coded by E6-ORF and E7-ORF, respectively.

Many attempts have been made to stimulate the immune system over cells associated to papilloma viruses and sequences thereof, respectively. However, these attempts have not yet yielded satisfactory results.

Therefore, it is the object of the present invention to provide a product serving for activating the immune system to identify and eliminate cells, particularly tumor cells,

associated to papilloma viruses and sequences thereof, respectively.

According to the invention this is achieved by the subject matters defined in the claims.

Thus, the subject matter of the present invention relates to a vector having a nucleic acid coding for a fusion polypeptide, the fusion polypeptide comprising a structural papilloma virus (poly)peptide and a non-transforming (poly)peptide coded by an early papilloma virus gene.

The expression "vector" comprises any vector which is suitable for gene transfer, i.e. the introduction of nucleic acids into cells. The vector may remain episomally within the cells or be integrated within the genome. Moreover, the vector may be a plasmid or virus vector. Examples of a virus vector are retroviral, adenovirus, vacciniavirus or adeno-associated virus (AAV) vectors, the latter being preferred. An AAV vector may be present in wild-type or modified form. It can also comprise only those sequences such as ITR sequences, that are necessary for its transduction ability. However, it can also be favorable for it to comprise additionally those sequences, such as rep sequences, which render possible for it the integration into chromosome 19. A virus vector can be present as viral particle or in the form of its nucleic acid. It is preferred for the virus vector to be replication-defective.

The expression "papilloma virus" comprises any papilloma viruses or sequences thereof, which can be associated with cells, particularly tumor cells. In particular, HPVs and more particularly "high risk" HPVs, such as HPV 16, 18, 33, 35 and 45, may be concerned.

The expression "nucleic acid" comprises any nucleic acid such as DNA and/or RNA, which codes for a fusion polypeptide comprising a structural papilloma virus (poly)peptide and a non-transforming (poly)peptide coded by an early papilloma

virus gene. It is favorable for the nucleic acid to be expressible. It is particularly favorable for it to be controlled by a constitutive or inducible promoter such as a tissue-specific or tumor-specific promoter.

The expression "structural papilloma virus (poly)peptide" comprises any peptide and polypeptide, respectively, of a papilloma virus, which is at least jointly responsible for the structure of the papilloma virus. In particular, such a (poly)peptide is coded by L1-ORF or L2-ORF of a papilloma virus and by part thereof, respectively. A (poly)peptide which can be present as VLP is particularly preferred.

The expression "a non-transforming (poly)peptide encoded by an early papilloma virus gene" comprises any peptide and polypeptide, respectively, which is coded by an early papilloma virus gene, particularly E1-, E2-, E4-, E5-, E6- or E7-ORF and by part thereof, respectively, and is non-transforming. The expression "non-transforming" refers to the fact that the (poly)peptide has no transformation ability by nature or by intervention. A preferred (poly)peptide is coded by E6-ORF or E7-ORF of a papilloma virus and by part thereof, respectively.

The expression "fusion polypeptide" refers to the fact that the structural papilloma virus (poly)peptide and the non-transforming (poly)peptide coded by an early papilloma virus gene can be present in any combination within the fusion polypeptide. The individual (poly)peptides may also originate from different papilloma viruses. The C terminus of the structural (poly)peptides is preferably connected with the N terminus of the non-transforming (poly)peptide. In addition, it may be advantageous for the non-transforming (poly)peptide to be localized within the structural (poly)peptide. A preferred fusion polypeptide comprises a (poly)peptide coded by HPV 16L1-ORF and a (poly)peptide coded by HPV 16 E6-ORF and E7-ORF, respectively. Furthermore, a fusion polypeptide is preferred which comprises a (poly)peptide coded by HPV 18 L1-ORF and a

(poly)peptide coded by HPV 18 E6-ORF and E7-ORF, respectively.

Common methods can be carried out for the preparation of an above vector. For example, an AAV vector can be prepared as virus particle as follows: The 5' end of the HPV 16 E6-ORF is ligated to the 3' end of the HPV 16 L1-ORF. Part of the E6-ORF had been deleted beforehand, so that the transforming properties of E6 were destroyed. The DNA fragment L1-ORF-E6-ORF is inserted in an AAV vector which contains the 5'-ITR and 3'-ITR sequences of AAV but not the sequences coding for the AAV Rep and AAV Cap proteins. The insertion is made between the two ITR sequences. The DNA fragment L1-ORF-E6-ORF is controlled by a promoter heterologous with respect to AAV. The resulting AAV vector is transfected in cells, which express the AAV Rep and AAV-Cap proteins. Furthermore, the cells are infected with a helper virus, e.g. adenovirus, so that the AAV vector is obtained as viral particle.

The immune system can be activated with an above vector, to identify and eliminate cells, particularly tumor cells, associated to papilloma viruses and sequences thereof, respectively. This can be achieved prophylactically and in a treatment. For this purpose, cells of the particular organism, such as antigen-presenting cells, e.g. dendritic cells, B cells, macrophages and/or tumor cells and/or pre-tumor cells, associated to papilloma viruses and sequences thereof, respectively, are transduced with the vector. The transduction can be made by common methods. If the vector is available as virus particle, it will be favorable to infect the cells therewith. On the other hand, if it is available as nucleic acid, e.g. DNA, it will be advisable to transfect the cells therewith. Electroporation, lipofection and particle gun have to be mentioned as transfection techniques by way of example. The cells may be present in the organism. On the other hand, the cells to be transduced can also be isolated from the organism, be transduced outside the organism and then be returned to the organism again. Such cells are referred to as autologous cells. Moreover,

allogenic cells can also be used for the transduction regarding the organism. In this connection, it is favorable for these cells to belong to an HLA type corresponding to the organism. The person skilled in the art is familiar with processes of providing cells with a certain HLA type. In addition, it is favorable if, in an above process, the tumor cells or pre-tumor cells are inactivated before they are returned to the organism. For this purpose, common methods, such as irradiation, can be carried out.

Another subject matter of the present invention relates to a vaccination agent which comprises an above vector and common auxiliary substances, such as buffers, diluents, carriers, etc. It can be favorable for the vaccination agent to contain further substances which can activate the immune system, e.g. against tumor cells. Such substances can be particularly MHC-1 molecules, co-stimulatory molecules, e.g. B7, and secretory immunostimulators, e.g. cytokines, such as IL-2, IL-12, interferon and GM-CSF. The substances can be present e.g. in the form of peptides, particularly synthetic peptides. The substances can also be present in the form of expression plasmids encoding them, which can also code for HLA molecules. It is particularly favorable for the vaccination agent to also contain the cells transduced by the vector. The above explanations apply to the cells. If tumor or pre-tumor cells are concerned, it will be favorable for the cells to be inactivated.

By means of the present invention it is possible to activate the immune system against cells which are associated to papilloma viruses and sequences thereof, respectively. These cells can be tumor cells and pre-tumor cells, respectively. The activation of the immune system can be made prophylactically and in the treatment. The present invention represents a new step of treating the most severe diseases via an *in vivo* gene therapy and *ex vivo* gene therapy, respectively.

The invention is explained by the below example.

Example: Preparation of a vector coding for an HPV16 L1-E7 fusion polypeptide

The L1-ORF of a genomic HPV16 clone (cf. Kirnbauer et al., (1993), 6929-6936) was amplified by PCR reaction. For this purpose, L1-specific primers were used which have an additional BglII restriction site at the 5' end. The amplified DNA fragment was cleaved using BglII and inserted in the BamHI restriction site of the common vector pUC19. An EcoRV restriction site, followed by a translation stop codon (TAA), was introduced at position 7051 of the L1-ORF by specific mutagenesis. By this, it was achieved that the L1-ORF coded for an L1 which was lacking the last 34 amino acids.

In another PCR reaction, the part of the E7-ORF of HPV16 was amplified which codes for the first 50 amino acids of E7. The employed primers included an EcoRV restriction site at their 5' end. The amplified DNA fragment was inserted in the EcoRV restriction site of the above pUC19 vector which codes for the shortened L1. Thus, an L1-E7 fusion gene was obtained. It was inserted in the common baculovirus vector pVL1392 via XbaI/SmaI. The L1-E7 fusion gene was cleaved therefrom by NotI/SmaI and inserted in the NotI restriction site of the AAV vector pUF2 (cf. Zolotukhin et al., J. Virol. 70, (1996), 4646-4654). A vector was obtained which codes for an HPV16 L1-E7 fusion polypeptide. Viral particles of the vector were obtained according to common methods (cf. Rolling and Samulski, Molecular Biotechnology 3, (1995), 9-15).

Article 34

Amended Claims

1. An AAV vector having a nucleic acid coding for a fusion polypeptide, the fusion polypeptide comprising a structural papilloma virus (poly)peptide and a non-transforming (poly)peptide coded by an early papilloma virus gene.

2. The vector according to claim 1, characterized in that the papilloma virus is a HPV.

3. The vector according to claim 2, characterized in that the HPV is selected from the group consisting of HPV 16, 18, 33, 35 and 45.

4. The vector according to any one of claims 1 to 3, characterized in that the nucleic acid is under the control of a constitutive or inducible promoter.

5. The vector according to claim 4, characterized in that the promoter is a tissue-specific or tumor-specific promoter.

6. The vector according to any one of claims 1 to 5, characterized in that the structural papilloma virus (poly)peptide is coded by L1-ORF and by part thereof, respectively.

7. The vector according to any one of claims 1 to 6, characterized in that the non-transforming (poly)peptide coded by an early papilloma virus gene is coded by E6-ORF or E7-ORF and by part thereof, respectively.

8. A vaccination agent containing the vector according to any one of claims 1 to 7 and conventional auxiliary agents.

9. The vaccination agent according to claim 8, characterized in that further substances activating the immune system are present.

10. The vaccination agent according to claim 8 or 9, characterized in that the vector is present in cells.

11. The vaccination agent according to claim 10, characterized in that the cells are tumor cells and/or pre-tumor cells, which are associated to papilloma viruses and sequences thereof, respectively.

12. The vaccination agent according to claim 11, characterized in that the tumor cells and the pre-tumor cells are inactivated.

13. Use of the vector according to any one of claims 1 to 7 and the vaccination agent according to any one of claims 8 to 12 for activating the immune system against cells associated to papilloma viruses and sequences thereof, respectively.

Abstract of the Disclosure

A vector is disclosed for a nucleic acid which codes for a fusion polypeptide which includes a structural papilloma virus (poly)peptide and a non-transforming (poly)peptide coded by an early papilloma virus gene.

Also disclosed is a vaccination agent which contains such a vector and the use of the vector and vaccination agent.

K 2639

4121-107

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

Application: United States Patent Application filed on February 1, 1999 in the United States Patent and Trademark Office as a Designated/Elected Office (DO/EO/US) under the provisions of 35 USC §371, based on PCT international application no. PCT/DE97/01629 filed on 30 July 1997, and claiming priority of German patent application no. 196 31 357.0 filed 2 August 1996.

As the below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "**VECTOR FOR ACTIVATING THE IMMUNE SYSTEM AGAINST CELLS ASSOCIATED TO PAPILLOMA VIRUSES OR SEQUENCES THEREOF,**" described and claimed in the above-identified United States Patent Application filed February 1, 1999 in the United States Patent and Trademark Office under the provisions of 35 USC §371.

I hereby state that I have reviewed and understand the contents of the above-identified international application and United States patent application based thereon, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office information which is material to the examination of this United States patent application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate on the invention listed below which were filed within one year prior to the above-identified international patent application:
Prior Foreign Application(s)

196 31 357.0	Germany	2 August 1996	Yes
(Number)	(Country)	(Day/Month/Year Filed)	(Priority Claimed?)

I have also identified below any foreign application(s) for patent or inventor's certificate on the invention having a filing date more than one year before the filing date of the above-identified international patent application, or before the filing date of the above-identified foreign patent application from which priority is claimed:

none

(Number)	(Country)	(Day/Month/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this specification is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United

States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

none

(Application Number) (Filing Date) (Status-Patented, Pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

STEVEN J. HULTQUIST, REG. NO. 28,021
WILLIAM BARRETT, REG. NO. 42,296

All correspondence in connection with this application should be sent to:

Steven J. Hultquist
Intellectual Property/Technology Law
P. O. Box 14329
Research Triangle Park, NC 27709
Telephone: (919) 419-9350

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that ~~such willful false statements~~ may jeopardize the validity of the application or any patent issued thereon.

1.00

Full Name of sole or first inventor: **KLEINSCHMIDT, Jürgen**

Inventor's Signature J. Kleinschmidt Date 9.3.99

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for AU-06

Full Name of second inventor: **MÜLLER, Martin**

Inventor's Signature _____ Date 9.3.99

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